REMARKS

I. Description of the Invention

A number of years ago, the FDA issued a requirement that orally-inhaled aqueous products must be sterilized. This was primarily due to a number of deaths involving non-sterile albuterol sulfate. The traditional method of sterilizing such products involved heating to 120°C. However, this heat sterilization method was not viable for products that were chemically unstable, or for formulations that were otherwise unstable.

An alternative method to the heat sterilization method involved filtration through a 0.2 micron (i.e., 200nm) filter. Using such filters, the smallest sized bacteria would be bigger than the pore size of 0.2 microns and thus be retained on the surface of the filter. However, this method is used for homogeneous solutions in which there are no complications of filter clogging. The filter sterilization method was not used for suspensions because the dry particles in the suspensions were too large to pass through the filter pores.

In the present invention, Applicants employed nanoparticulate technology by media milling a suspension of a poorly water soluble therapeutic agent in a surface modifier, thus making crystalline particles that are submicron in size (claim 28). As described in Examples 1 and 2 and in Tables I-III, the resulting submicron particles were then formed into aerosols and nebulized. As explained on page 2 of the specification, simply knowing that smaller droplets of aerosols can be delivered deeper into the respiratory system does not solve the problem of incorporating sufficient therapeutic agent into the aerosol to be efficient, particularly where the therapeutic agent is only slightly soluble in the liquid for the aerosol. As shown in the Examples and Results of the Specification (see nebulization studies and rabbit study), Applicants' invention was indeed effective in delivering sufficient amounts of the aerosol containing the poorly water-soluble therapeutic agent. In addition, such a composition could be subjected to sterile filtration, thus satisfying the FDA requirements.

II. Examiner Interview

Applicants' attorney, Teresa Bittenbender would like to thank Examiner Qazi for her time and kindness towards Inventor Bosch and Ms. Bittenbender during the interview on

August 30, 2007. As requested by Examiner Qazi, Applicants are clearly setting forth the above description of the invention as well as specification support for the currently amended claims. In addition, the claims have been amended as discussed in the Interview and as consistent with the parent patent, now issued, to refer to an average droplet size of 10 microns. Claim 28 has also been amended to refer to delivery to the lungs, which is consistent with an earlier restriction/election. Regarding the Examiner's statements of the written description rejection on method of delivery of an aerosol to the lungs, Applicants have amended Claim 28 as discussed to claim a method of treatment of a respiratory illness in a mammal.

III. Status of the Claims

In this Response, claims 28 and 44 are amended and claim 45 is cancelled. Upon entry of this Response, claims 28-40, 42-44, and 47-59 are pending and under examination.

Claim 28 as amended is directed to method of treating a respiratory illness in a mammal. Support is provided in the specification on page 3, lines 21-24. Amendment to claim 28 from average droplet size of 10 microns is supported in the specification on page 1, lines 22-29. In addition, claim 28 is amended to recite that the aerosol composition is administered to the lungs. Support can be found for this amendment on page 1, lines 22-29 and Example 2, page 24. Dependant claim 44 is amended to recite particular respiratory illnesses. Support is provided in the specification on page 3, lines 21-24.

Thus, no new matter is added.

IV. Rejection of the Claims Under 35 U.S.C. § 112, first paragraph

Claims 28-40, 42-45, and 47-50 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to meet the written description requirement. In particular, the claims are rejected because "Applicant had no possession at the time this application was filed of claimed 'method of delivering' and the steps as claimed . . . and method of treating respiratory illness such as AIDS, AIDS-related pneumonia, respiratory distress syndrome and various others listed in claim 44." Office Action at 4.

Claim 28 as amended is directed to a method of treating a respiratory illness in a mammal, and recites a droplet particle size of less than 10 microns, thus rendering the rejection moot. Support for this amendment can be found on page 3, lines 21-24 and on page 1, lines 23-29 of the specification. Withdrawal of rejection is respectfully requested.

Claim 44 as amended does not recite AIDS or AIDS related pneumonia. Withdrawal of rejection of claim 44 is respectfully requested.

Claim 45 has been cancelled, thus rendering all rejections moot with respect to that claim.

V. Rejection of the Claims Under 35 U.S.C. § 103(a)

Claims 28-40, 42-45 and 47-59 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over (1) Liversidge, in view of Folke Moren, and (2) Liversidge, in view of Gennaro and Dieter Kohler. Applicants respectfully traverse these grounds of rejection.

The Supreme Court recently reaffirmed the Graham factors for determining obviousness in *KSR Int'l Co. v. Teleflex Inc.* (No. 04-1350) (U.S., April 30, 2007). The Graham factors, as outlined by the Supreme Court in *Graham et al. v. John Deere Co. of Kansas City et al.,* 383 U.S. 1 (1966), are: 1) determining the scope and contents of the prior art; 2) ascertaining the differences between the claimed invention and the prior art; 3) resolving the level of ordinary skill in the pertinent art; and 4) evaluating evidence of secondary consideration. The Supreme Court held that the proper inquiry for determining obviousness is whether the improvement is more than the predictable use of prior art elements according to their established functions. The Court noted that it is "*important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] element" in the manner claimed*, and specifically stated:

> [o]ften, it will be necessary . . . to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed

> by the patent at issue. To facilitate review, this analysis should be made explicit.

KSR Int'l Co. v. Teleflex Inc., slip op. at 14 (emphasis added).

As discussed below, the differences between the prior art and the present application are so substantial, that the cited art cannot render the claimed invention obvious.

A. *Liversidge in view of Folke Moren*

Claims 28-40, 42-45 and 47-59 are rejected over Liversidge, in view of Folke Moren because "[i]t would have been obvious . . . to prepare the method of delivering an aerosol to lungs as claimed by the combined teachings of the two references cited above for the treatment of respiratory diseases by using aerosols because Liversidge et al teaches the average particle size, surface modifier, and all other limitations of the presently claimed invention and Moren teaches aerosols and delivery to respiratory tract using poorly soluble drugs such as steroids." Applicants respectfully disagree.

Moren describes some aqueous systems but teaches that one must choose a form of the drug that is soluble in water. *See*, Moren at section 4.1.1, page 340. In other words, Moren provides that in order for aqueous aerosols to be effective, the drug should be in solution. Furthermore, Moren states that a water soluble form of the drug should be used, and that it may be necessary to adjust the formulation to achieve adequate solubility by, for example, (1) changing the pH, (2) adding a cosolvent, (3) adding a surfactant to form micelles, or (4) forming inclusion complexes. But Moren points out that there are disadvantages to these approaches, such as changes in viscosity and surface tension (which affect aerosol generation), increases or decreases in the liquid evaporation rate (which will affect droplet size), irritation to mucosa, coughing, bronchospasm, and lack of drug availability from micelles. Moreover, Moren teaches that the probability of success when trying to aerosolize a suspension is quite low because of problems with physical stability, lack of redispersion, accuracy of dose, and problems with fragmenting the liquid.

Moren's teaching of various factors that must be considered when attempting to make an aerosol formulation of a poorly water-soluble drug, would lead one of ordinary skill in the

art to believe that it is highly preferable to utilize water-soluble drugs in aerosol formulations. Thus at the time the claimed invention was made there was no apparent reason to combine the prior art to make an aerosol formulation of a poorly water-soluble drug as presently claimed.

Claim 45 is cancelled, thus rendering all rejections moot with respect to that claim.

B. ***Liversidge, in view of Gennaro and Dieter Kohler***

Claims 28-40, 42-45 and 47-59 are as allegedly obvious over Liversidge in view of Gennaro and Dieter Kohler. In particular, the claims are rejected because "[i]t would have been obvious . . . to prepare the method of delivering an aerosol to lungs as claimed for treatment of respiratory diseases by the combined teachings of the above cited references, because Liversidge et al teaches the average particle size, surface modifier, and all other limitations of the presently claimed invention and Gennaro and Kohler references teach the use of aerosols for poorly soluble drugs and inhalation products and treatment of asthma and other respiratory illness." Office Action at 18-19. Applicants respectfully traverse this ground for rejection.

Kohler only generically describes aerosol formulations and is silent on the issue of inhaled particle size. Nothing in Kohler gives any indication or reason that one would want to make a nanoparticulate formulation of a drug and aerosolize it. In fact, Kohler teaches away from aqueous aerosols containing drug nanoparticles. The last sentence on page 310 (before Figure 3) states that "the water solubility of the drug and its viscosity determine the amount of drug available in the aerosol droplet after nebulization." This statement implies that the drug must be in solution to be suitable for nebulization as an aqueous aerosol. Applicants' instant invention is directed to a suspension (as referenced in claim 28 language of "crystalline particles which are poorly soluble in water"), not a solution as in Kohler. "Crystalline particles which are poorly soluble in water, when in water, are suspensions, not solutions. Kohler's only reference to aerosolization of solid particles is on p. 311, where he discusses delivery of solid particles from pressurized MDIs and dry powder inhaler systems. Accordingly, there is no suggestion that solid drug particles can be delivered by nebulization of aqueous suspensions.

Furthermore, Gennaro deals exclusively with aerosol formulations that contain propellants (specifically fluorocarbons, which are no longer in use). Although Gennaro does make brief reference to "Dispersions or Suspensions (Powder Aerosols)," Gennaro states that "the moisture content should be kept below 300 ppm and the propellants and solvents must be dried by passing them through a drying agent." Gennaro at 1672. Accordingly, Gennaro does not provide any reason to aerosolize aqueous suspensions. Further, claim 45 which was directed to propellants, has been cancelled.

Accordingly, one of skill in the art would have no apparent reason to combine Liversidge and Gennaro with the teachings in Kohler to make that which is claimed in instant claim 28.

CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

Respectfully submitted,

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